MSNOPL TSD Presentation

New products Validation & DMF details				
Sr.No	Product Name	Validation completion	DMF for US	DMF for EDQM
1)	VIBEGRON	29-04-2024	24-09-2024	Not done
2)	FOSFOMYCIN SODIUM	03-05-2024	29-09-2024	09-10-2024
3)	FOSFOMYCIN TROMETHAMINE	24-06-2024	27-09-2024	30-10-2024
4)	BELUMOSUDIL MESYLATE	09-07-2024	29-09-2024	Not done
5)	TAPINAROF	08-10-2024	28-11-2024	Not done
6)	AZATHIOPRINE *	22-08-2024	28-09-2024	08-11-2024
7)	LERCANIDIPINE HYDROCHLORIDE*	06-10-2024	10-01-2025	Not done
8)	LERCANIDIPINE HYDROCHLORIDE*	Feb -2025	To be filled	
9)	MAVACHEMTON	Feb -2025	To be filled	
10)	RESMETIROM	Marh-2025	To be filled	

* Validation at APIChem

BELUMOSUDIL MESYLATE

Total Revenue 13.82/- Cr (72.9 kg)

- Validation completed 09-07-2024.
- DMF Filing completed 29-09-2024
- Apotex delivery 29-11-24.

APOTEX

32.4 kg Dispatch Completed

- For Formulation 40Kg Order confirmed 23/10/24
- Campaign started on 16/10/24 and end 30/12/24
- Delivered 20Kg in 1st week Dec24.
- Next 20 Kg by 01/01/25.

40.5 kg Dispatch Completed

MSN Formulation

TAPINAROF

Total Revenue 1.52/- Cr (11.38 kg)

Pending 6-8 kg Dispatch by Feb25

- Validation completed - 08-10-2024
- DMF Filing completed - 28-11-2024
- Encube 10Kg delivery Dec-24.

Validation

10kg Dispatch Completed

- Batches under progress
- Dispatch commitment by FEB25

- Recent batches under execution
- COA planned on 11-02-25.

10 kg Pending PO

Commercial Batches

Future Requirements

Currently below equipment's brought from other unit

- 50 lts SS reactor
- 12 trays SS VTD
- 150m3/hour Oil ring Vacuum pump
- 500CFM dehumidifier

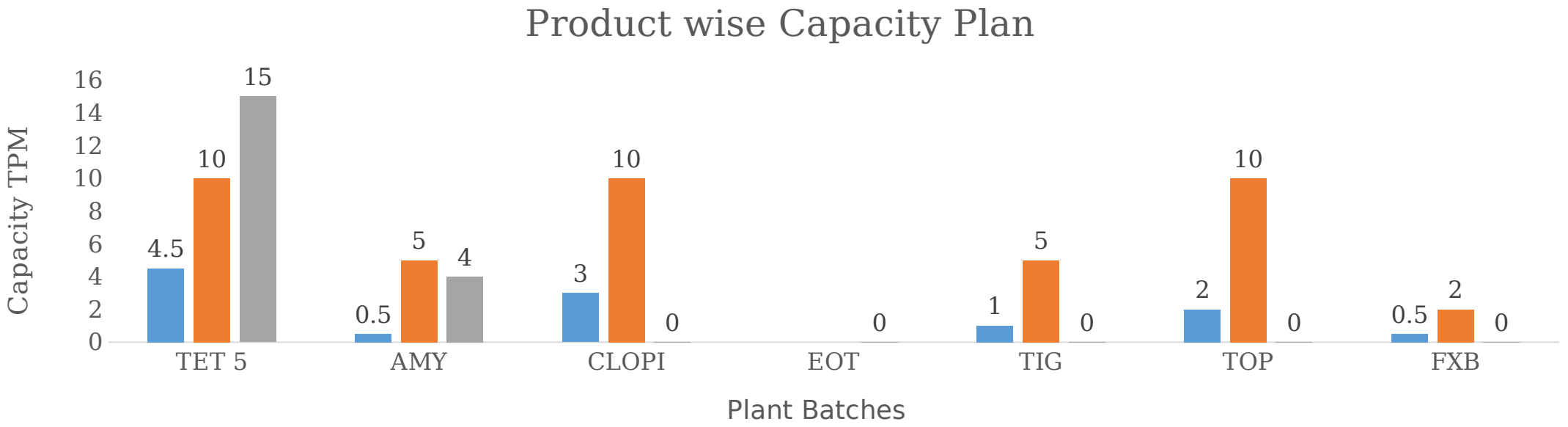
30 Lacs Capex required

Total Revenue 3.5/- Cr (10 kg)

Takeaways

- XRD is meeting but ,Higher MTBE in the initial batches due to 2 lots filtration with available filter .[Historically Kilo Lab filter used for filtration, 3 Lots]
- Higher MTBE content ,Resolved with 3 lots filtration by using Kilo lab 25L NF as 3rd filtration set up.
- Immediate action ,New Nutsche filter procured

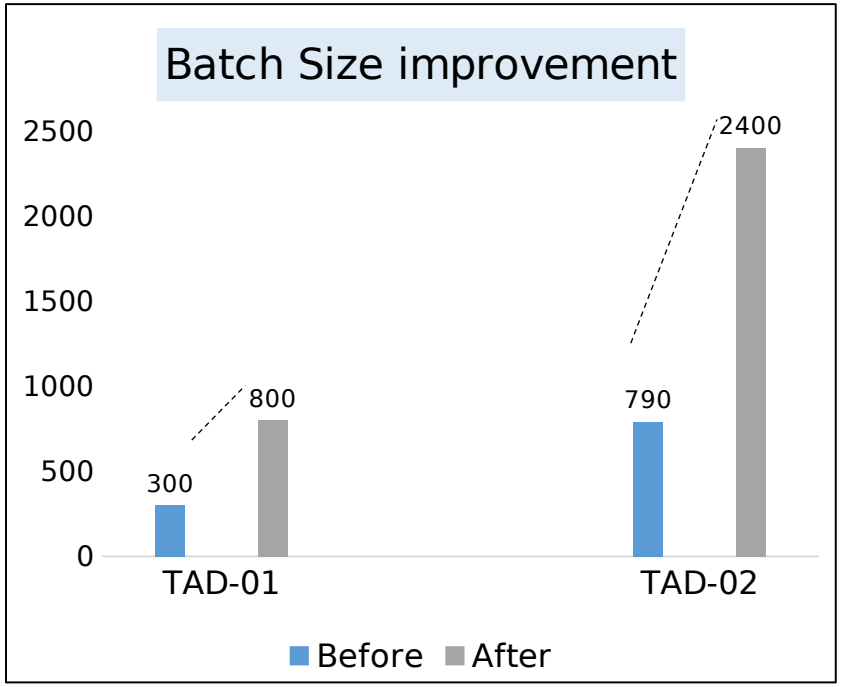
Sr.no	Product Name	Existing Capacity (TPM)	Proposed Capacity (TPM)	Remarks (TPM)
1	TAPENTADOL HYDROCHLORIDE (TET 5)	4.5	10	15 TPM achieved
2	ATOMOXETINE HYDROCHLORIDE (AMY)	0.5	8	To be demonstrated Batch size enhancement shall be planned based on future demand
3	CLOPIDOGREL BISULFATE (CLOPI)	3	10	*Decantation system proposal in place
4	ETIFOXINE HYDROCHLORIDE (EOT)	0.5	1	To be panned with CIP
5	TICAGRELOR (TIG)	1	5	To be assessed
6	TOPIRAMATE (TOP)	4	10	Opportunity – up to 8TPM
7	FEBUXOSTAT (FXB)	0.5	2	To be assessed

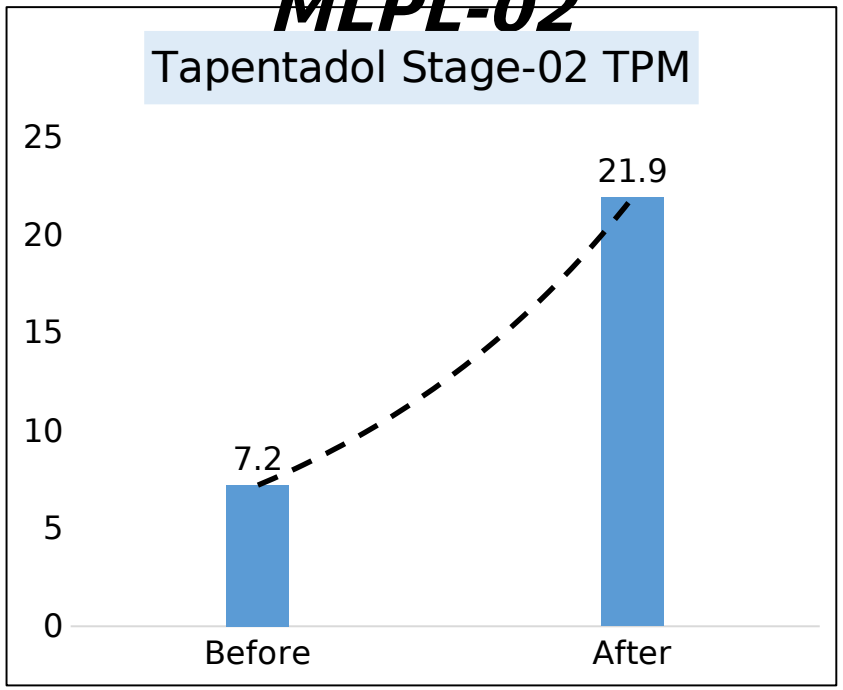


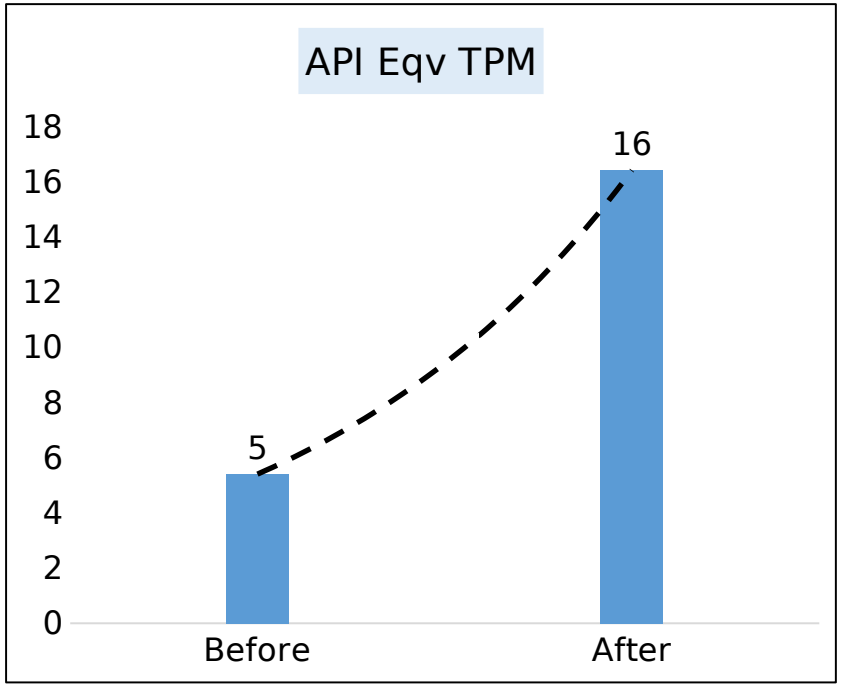
Summary of Implementations at MLPL-2 Site

S.No	Improvement	Benefit	Savings/ Annum
1	Batch size improvement of Tapentadol Intermediate stage-01 from 300 Kg to 800 Kg.	1) Increased delivery of Tapentadol intermediate stage-02 from 7TPM to ~20TPM by capacity enhancement. 2) Utilization of existing capacity.	-
2	Batch Size improvement of Tapentadol intermediate stage-02 from 790 Kg to ~ 2400Kg		
3	Improvement in addition time of Ethyl acetate layer into DBTA soln. for resolution process using dedicated receiver, lines and high efficiency pump	1) Reduction in formation of gummy mass at resolution process thus improving the solid nature after filtration. 2) Ethyl acetate layer addition time completed in 10 mins	-
4	Implementation of Steam control valve for Tapentadol stage-01 reactors for Heating, Maintenance and distillation operations	1) Reduced human intervention at plant operations by semi-automation. 2) Reduced cycle times for Heating and distillation operations	₹ 3,12,828
5	Implementation of Utility Flow control valve for Grignard reactors for Reaction mass temperature controlling during M-500 lot-01 & 02 addition.	1) Reduced human intervention at plant operations by semi-automation. 2) Reduced cycle times for M-500 addition from ~48 hrs. to ~24hrs. 3) Elimination of vapor loss of M-500 during addition	₹ 10,86,210
6	Implementation of deep blow leg into the reaction mass for M-500 addition for Grignard reactors, to avoid vapor loss and reduce addition time.		
7	Implementation of dedicated 2" lines for 3 Grignard reactors for transferring the Rxn mass for quenching operation in 2 reactors.	1) Reduced human intervention for repeated temporary line arrangements 2) Reduced cycle time for quenching operation from ~8 hrs. to ~3hrs	₹ 4,34,484
8	Implementation of 60 KVA UPS for 3 resolution reactors to avoid tripping of reactors during power failure or power change overs	1) No Breakdowns of resolution reactors after UPS Installation..	

Tapentadol Capacity Enhancement at MLPL-02

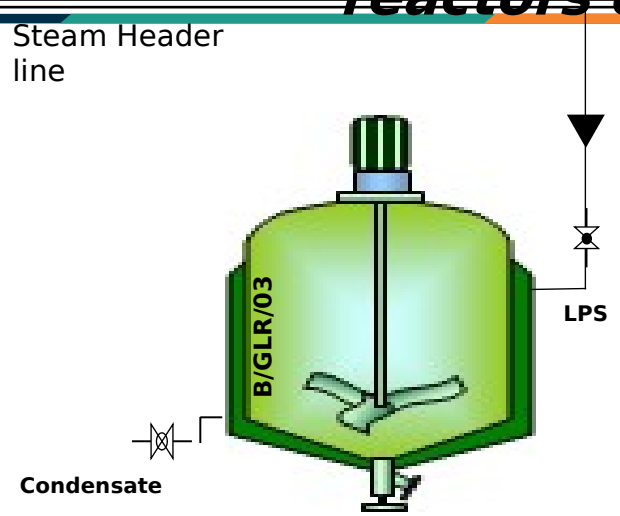


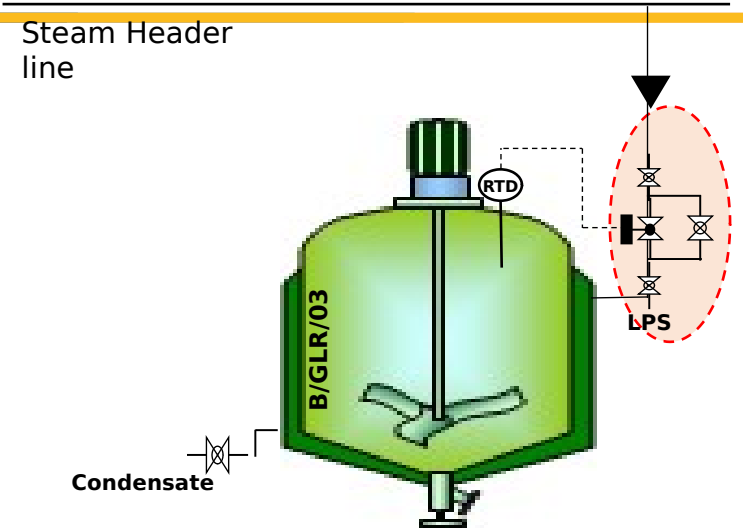




- Tapentadol stage-01 & 02 existing batch size has been increased from 300Kg and 790 Kg respectively to 800 Kg stage-01 and ~2400Kg stage-02 by using new facility (B block) i.e. 8KL, 10KL GLR & SSR reactors.
- For filtration and drying of TAD-01 salt, 5.0KL ANFD is being used in the current facility compared to CFG & ATD in the previous facility.
- Increased batch size for Tapentadol stage-01 & 02 has also led to capacity enhancement at MLPL-02 facility and delivery of Tapentadol API equivalent.

Implementation of steam control valve for 2 reactors of TAD-01





Before: Use of globe valve for steam application

- Earlier application of steam for TAD-01 reaction mass for heating and distillation operations was done manually using globe valve. Personnel intervention was more to monitor the temperature according to the process requirements

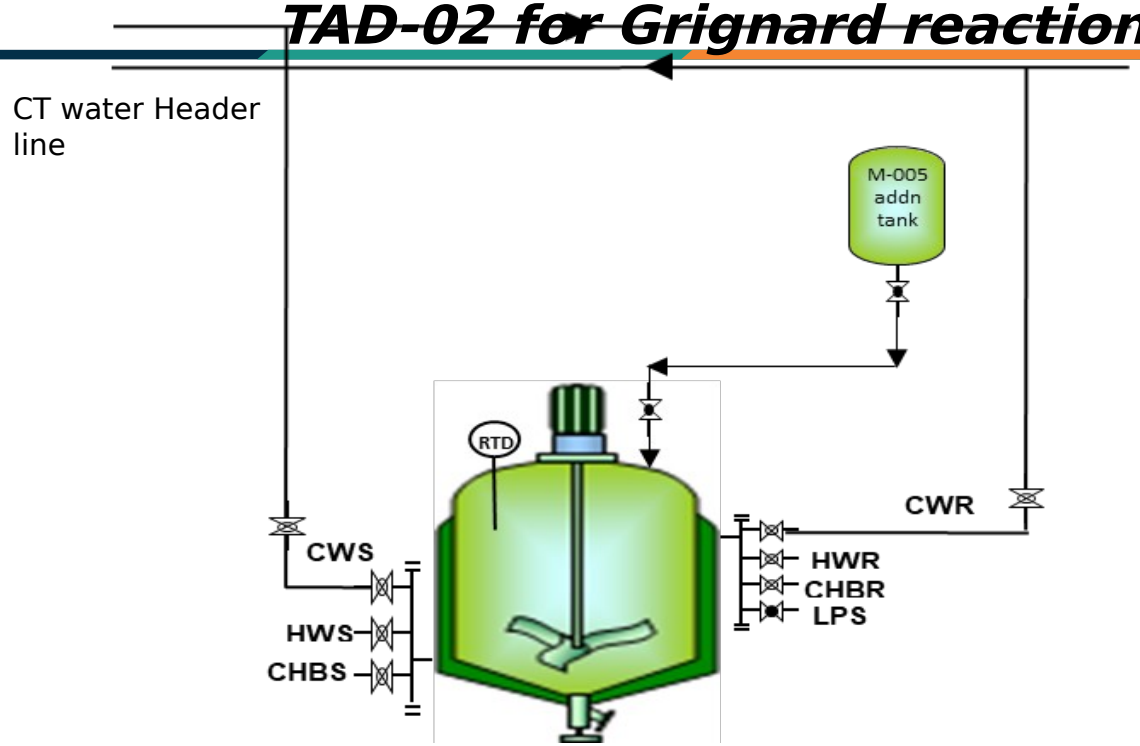
After: Use of steam control valve for steam application

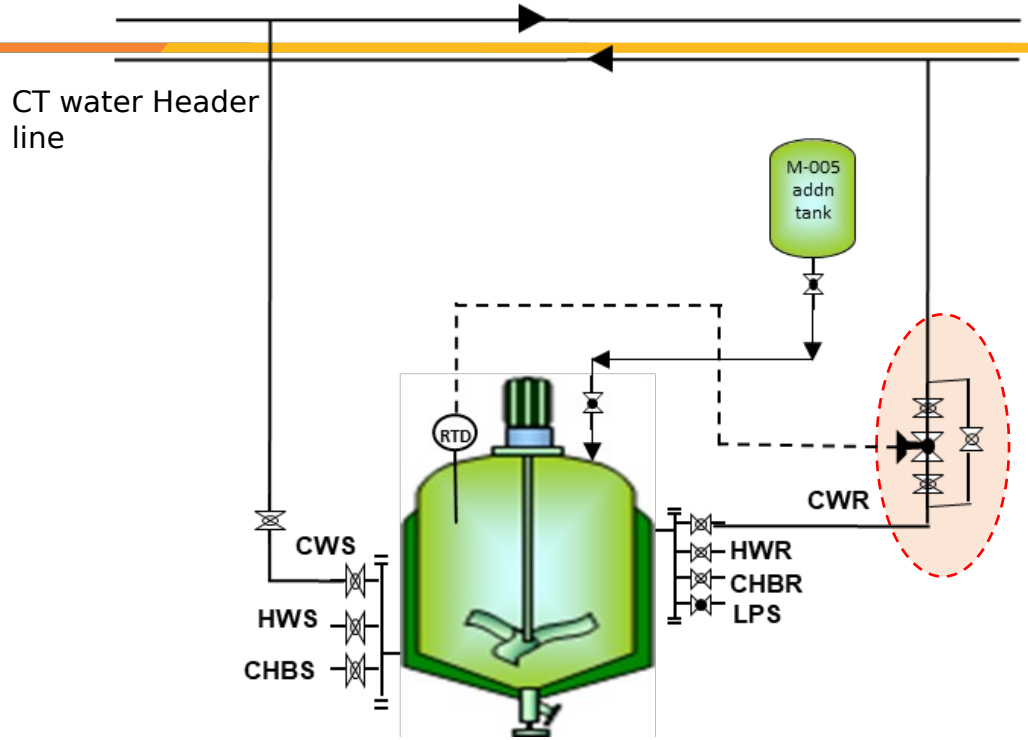
- After implementation of steam control valve for 2 no's TAD-01 reactors, steam application for heating, reaction maintenance and distillation is done using control valve. Personnel intervention was reduced after automating the steam application.

Benefits: Usage of steam control valve with preferred set point of temperature for Heating, reaction maintenance & Distillation operation has reduced the cycle times as tabulated below:

S.No	Operation	Existing Cycle Time (Hr)	Reduced Cycle time (Hr)	Difference (Hr)	Man-hours/ batch /month	Man-hours/ annum	Cost savings/Month on Agitator running time	Cost savings/Annum on Agitator running time
1	Heating	4	2	2	80	**2880**	₹ 26,069	₹ **3,12,828**
2	Distillation	9	5	4	160			

Implementation of utility Flow control valve for 2 reactors of TAD-02 for Grignard reaction





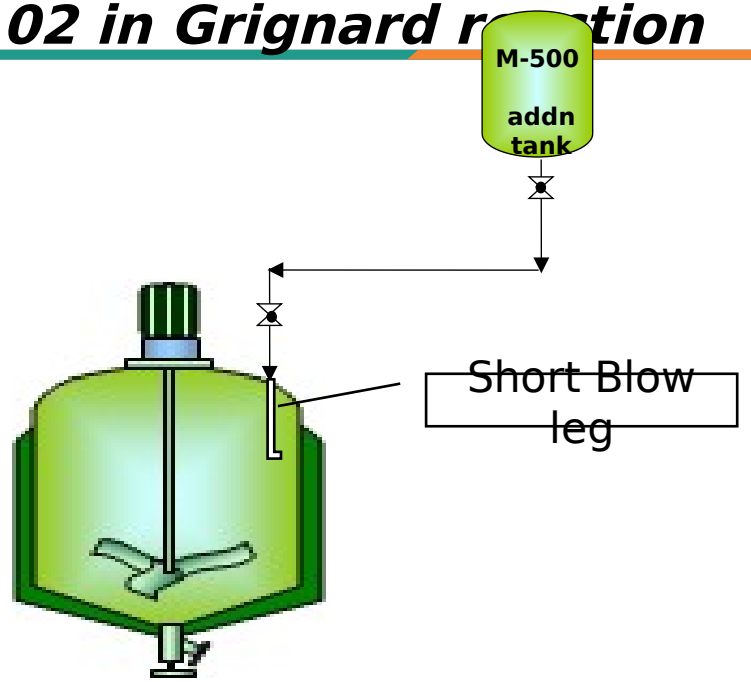
Before: Use of globe valve for CT water circulation for reaction mass temperature controlling during M-500 addition

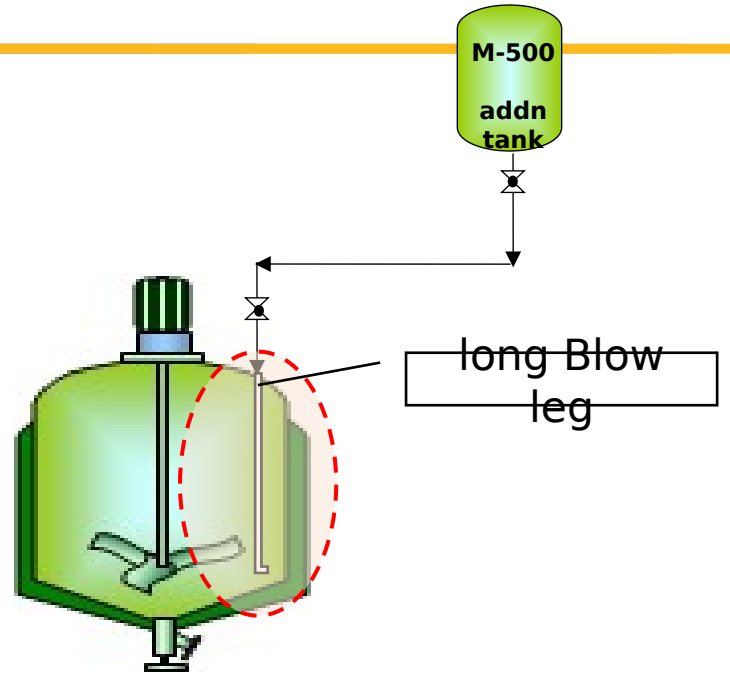
- Earlier for M-500 addition, CT water circulation was controlled manually w.r.t to process temperature. Round the clock monitoring was required during M-500 addition to avoid deviation of process conditions.
- Also, M-500 addition took about 48-50 hrs for lot-01 and lot-02 addition.

After: Use of Utility flow Control valve for CT water circulation for reaction mass temperature controlling during M-500 addition

- After implementation of control valve for utility return lines, M-500 addition temperature is maintained by providing set point at RTD sensor for RXN mass with feedback loop to control valve at utility return line
- M-500 addition time reduced to about 26-28 hrs.

Implementation of deep blow leg for M-500 addition line for TAD-02 in Grignard reaction





Before: For M-500 addition in Grignard reactors, use of short length J-bend at process condition 55±5 °C led to vapour loss of M-500 leading to unconverted stage-01 material at TLC. This also led to slow rate of M-500 addition increasing the cycle time at Grignard operation.

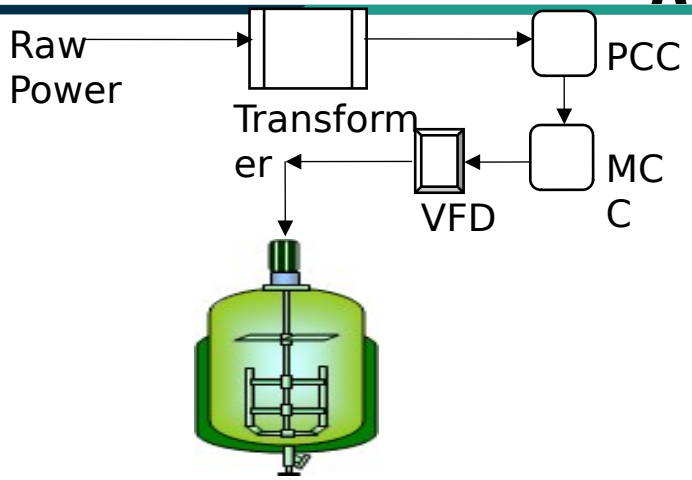
After: By implementation of deep blow leg into the reaction mass for M-500 addition vapour loss could be avoided, thus ethyl bromide addition rate was increased and cycle time at Grignard operation was reduced.

Benefits: By implementation of control valve at utility return line and blow leg for Grignard reactors, M-500 addition cycle time was reduced from avg of 48-50 hrs to 26-28 hrs. This combined modification at Grignard operation has benefits in terms of energy and man hours saving as tabulated below.

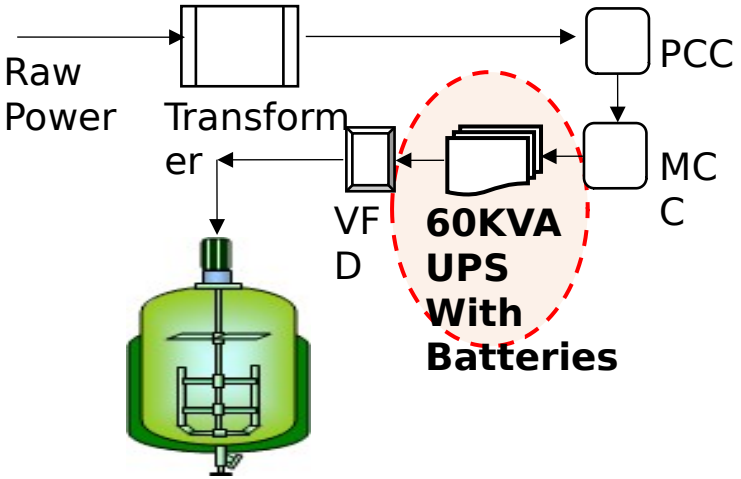
Combined savings on Grignard process by implementation of control valve and blow leg for M-500 addition.

S.No	Operation	Existing Cycle Time (Hr)	Reduced Cycle time (Hr)	Difference (Hr)	Man-hours/ batch /month	Man-hours/ annum	Cost savings/Month on Agitator running time	Cost savings/Annum on Agitator running time
	M-500 Addition						₹	₹

Installation of 60-KVA UPS for 3 no's Resolution reactors



Before



After

In Resolution process with batch size of 800Kg, occupancy of the reactor is ~75% with about 70-75%% power load on agitator. Nature of the resolution mass is gummy in nature during the initial stage of resolution process and has very high settling velocity.

In-case of any power failure or power change over, Reaction mass solids get settled at the bottom of reactor and agitator gets tripped within a fraction of ~20Sec. During start-up of the agitator, power load goes up to 100Amps on DOL which is not favourable for smooth operation of any motor.

In such cases of such reactor breakdowns there is a productivity loss which is tabulated below based on previous trend

S. No	Activity	Units	
1	TAD-01 BCF	18	Hrs
2	No. of Batches/Month	40	No.s
3	No. of Resolution reactors	4	No's
4	Avg No. of Batches Executed in each reactor	10	No's
5	No. of Breakdowns (for 4 resolution reactors) in the month of Sept'24 & Oct'24	14	
6	Average downtime per reactor	1	day
7	Productivity loss during down time	336	Hrs
		7	No. of Batches at resolution process
		16800	TAD-01 (Kgs)
		5121	TAD-02 (Kgs)

Such Breakdowns of Resolution reactors was minimized by installation of 60 KVA UPS to overcome the trip issues and perform the 48hrs of resolution process without any power interruptions.

Sr. no	Design Improvements	Action plan	P&ID attachment
1	Trifluoroacetic anhydride Charging	Provided new acid-resistant fume chamber has been installed for pumping TFAA using an AODD pump, with the top outlet seamlessly connected to the scrubber system for efficient fume management.	A-block TFAA P&ID
2	Centrifugation	Centrifuges are connected to the scrubber system via a "reverse umbrella" setup to ensure fumes capture & control.	F-Block CFG system
3	Ethyl acetate distillation setup	A secondary condenser with chilled brine utilities has been installed on the A/SSR/11 reactor to reduce distillation cycle time effectively.	A- Block EA Distillation setup
4	Centrifugation Ml's Transferring	Provided AODD pump for Ml's transferring instead of Centrifugal pump or vacuum system	Centrifugation rasferring syster
5	Scrubber Connection for drier	Provided Scrubber connection system for Drying block for selective drier	crubber system for G-Block drier
6	Ethyl HCl Charging	provided new acid-resistant fume chamber has been installed for pumping E.A HCl using an AODD pump, with the top outlet seamlessly connected to the scrubber system for efficient fume management.	.A HCL Charging System
7	HBr Distillation setup with steam controller	Provided Steam controller valve for heating, Maintenance & Secondary graphite condenser for effective distillate collection	HBr distillation steam controlle
8	HBr reaction reverse quenching system	Provided reverse quenching system for reducing quenching duration	HBr Rxn Reverse uenching syster
9	Ethyl acetate Sub-cooler system	Proposal for Sub-cooler for the distillate to eliminate the vapor loss.	EA distillatin ubcooler system
10	Water ring Vacuum pump with intercooler setup in D block	Provided water ring vacuum system with in-house inter-cooler setup.	Water ring uum pump syst